

We claim:

1. A particulate composition for delivery to the pulmonary system comprising:
5 hollow and porous particles comprising a phospholipid and a polyvalent cation in an amount effective to increase the gel-to-liquid crystal transition temperature of the particle compared to particles without the polyvalent cation.
2. A particulate composition according to claim 1 wherein said gel-to-liquid crystal
10 transition temperature is greater than the storage temperature for said composition by at least 20 °C.
3. A particulate composition according to claim 2 wherein said gel-to-liquid crystal
15 transition temperature is greater than the storage temperature for said composition by at least 40 °C.
4. A particulate composition according to claim 1 further comprising a surfactant selected
20 from the group consisting of nonionic detergents, nonionic block copolymers, ionic surfactants and combinations thereof
5. A particulate composition according to claim 4 wherein the surfactant is selected from
the group consisting of sorbitan esters, ethoxylated sorbitan esters, fatty acids, salts, sugar
esters, ethylene oxides, and combinations thereof.
- 25 6. A particulate composition according to claim 1 wherein the phospholipid comprises a saturated phospholipid.
7. A particulate composition according to claim 6 wherein the phospholipid comprises
30 dipalmitoylphosphatidylcholine or distearoylphosphatidylcholine.
8. A particulate composition according to claim 1 wherein the polyvalent cation is a
divalent cation.
9. A particulate composition according to claim 8 wherein the divalent cation is selected
35 from the group consisting of calcium, magnesium, or zinc.

10. A particulate composition according to claim 8 wherein the molar ratio of divalent cation to surfactant is at least 0.05.

5 11. A particulate composition according to claim 10 wherein the molar ratio of divalent cation to surfactant is 0.05 – 2.0.

12. A particulate composition according to claim 10 wherein the molar ratio of divalent cation to surfactant is 0.25 – 1.0.

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13. A particulate composition according to claim 12 wherein the divalent cation is calcium.

14. A particulate composition according to claim 13 wherein the molar ratio of calcium to surfactant is about 0.50.

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15. A particulate composition according to claim 1 wherein the phospholipid comprises a natural or synthetic lung surfactant.

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16. A particulate composition according to claim 1 further comprising 0.1 – 80% w/w of an active agent.

17. A particulate composition according to claim 16 wherein the active agent is selected from the group consisting of nicotine, human growth hormone, parathyroid hormone, leuprolide, budesonide, tobramycin, albuterol, and salts thereof.

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18. A particulate composition according to claim 1 further comprising a polymer selected from the group consisting of polysaccharides, polyvinyl alcohol, polyvinyl pyrrolidone, polylactides, polyglycolides, polyethylene glycol, or mixtures thereof.

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19. A particulate composition according to claim 1 comprising particles having a mass median diameter of less than 20 microns.

20. A particulate composition according to claim 19 wherein the mass median diameter is within 0.5 – 5 microns.

21. A particulate composition according to claim 19 wherein the particles comprise an aerodynamic diameter of less than 10 microns.

5 22. A particulate composition according to claim 21 wherein the aerodynamic diameter is within 0.5 – 5 microns.

23. A particulate composition according to claim 1 comprising an emitted dose of at least 40%.

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24. A particulate composition according to claim 1 comprising an emitted dose of at least 60%.

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25. A particulate composition according to claim 1 comprising an emitted dose of at least 90%.

26. A particulate composition according to claim 1 further comprising a non-aqueous suspension medium.

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27. A particulate composition according to claim 1 further comprising an excipient selected from the group consisting of amino acids, carbohydrates, inorganic salts, organic salts, carboxylic acids, and mixtures thereof.

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28. A particulate composition according to claim 27 wherein the excipient is selected from the group consisting of hydrophobic amino acids, monosaccharides, disaccharides, polysaccharides, sodium citrate, citric acid, ammonium carbonate, ammonium acetate, and ammonium chloride.

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29. A particulate composition according to claim 1 further comprising a density of less than 0.5 g/cm³.

30. A particulate composition according to claim 29 wherein the density is less than 0.05 g/cm³

31. A particulate composition for delivery to the pulmonary system comprising:
hollow and porous biodegradable particles comprising a gel-to-liquid transition temperature
T_m and a storage temperature T_s wherein T_m > T_s by at least 20 °C.

5 32. A particulate composition for delivery to the pulmonary system comprising:
20 – 99.9% phospholipid;
a polyvalent cation in an amount effective to increase the gel-to-liquid crystal
transition temperature of the particle compared to particles without the polyvalent cation; and,
optionally
10 0.1 – 80% active agent;
wherein the composition is in the form of hollow and porous particles.

33. A method for producing a phospholipid particulate composition comprising:
adding a polyvalent cation to a formulation comprising a phospholipid;
15 drying said formulation to form a dry particulate composition comprising hollow and
porous particles.

34. A method according to claim 33 wherein the particulate composition comprises
particles having a mass median diameter of less than 20 microns.
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35. A method according to claim 34 wherein the mass median diameter is within 0.5 – 5
microns.

36. A method according to claim 35 wherein the particles comprise an aerodynamic
25 diameter of less than 10 microns.

37. A method according to claim 36 wherein the aerodynamic diameter is within 0.5 – 5
microns.

30 38. A method according to claim 33 wherein the drying step is performed by spray drying.

39. A method according to claim 38 wherein the spray drying process comprises adding a
blowing agent to the feedstock.

40. A method according to claim 38 wherein the feedstock comprises a colloidal solution or suspension.
41. A method according to claim 40 wherein the polyvalent cation is added to the
5 feedstock at a molar ratio of cation:phospholipid of 0.25-1.0
42. A method according to claim 41 wherein the polyvalent cation is added to the feedstock as calcium chloride.
- 10 44. A method for delivery to the pulmonary system comprising administering to the respiratory tract of a patient in need of treatment an effective amount of hollow and porous particles comprising phospholipid and a polyvalent cation present in an amount effective to increase the gel-to-liquid crystal transition temperature of the particle compared to particles without the polyvalent cation.
- 15 45. A method according to claim 44 wherein the particulate composition comprises particles having a mass median diameter of less than 20 microns.
46. A method according to claim 45 wherein the mass median diameter is within 0.5 – 5
20 microns.
47. A method according to claim 45 wherein the particles comprise an aerodynamic diameter of less than 10 microns.
- 25 48. A method according to claim 47 wherein the aerodynamic diameter is within 0.5 – 5 microns.
49. A method according to claim 44 wherein the particles comprise polyvalent cation at a molar ratio of cation:phospholipid of 0.25-1.0
- 30 50. A method according to claim 49 wherein the polyvalent cation comprises calcium.
51. A method according to claim 48 wherein the particles comprise a density of less than 0.5 g/cm^3 .

52. A method according to claim 51 wherein the particles further comprise an active agent selected from the group consisting of nicotine, human growth hormone, parathyroid hormone, leuprolide, budesonide, tobramycin, albuterol, and salts thereof.

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